Myocardial contractility and perfusion in healthy volunteers and patients with dilated cardiomyopathy

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SUMMARY

In this thesis some of the pathophysiological processes that are involved in heart failure, especially due to idiopathic dilated cardiomyopathy, are described. Patients as well as healthy volunteers were investigated with two imaging techniques, positron emission tomography and dobutamine stress echocardiography. Myocardial perfusion and b-adrenoceptor density were measured with positron emission tomography while contractile responses were studied using dobutamine stress echocardiography. The development of the techniques used for investigation of the subjects is reviewed and the results of the measurements in patients are described in this thesis.

The first two chapters describe myocardial perfusion measurements with positron emission tomography in healthy volunteers and patients with left ventricular dysfunction, both with and without signs of heart failure. The first chapter shows that positron emission tomography with [^{13}N]ammonia can be used to perform measurements of myocardial perfusion in humans. Previous studies of myocardial perfusion using [^{13}N]ammonia and positron emission tomography did not use positron emission tomography to its full potential and perfusion was only studied in a semiquantitative way, i.e. static positron emission tomography. Images obtained this way showed an unexplained reduced uptake in the posterolateral part of the heart in healthy volunteers without coronary artery disease, in whom a homogeneous uptake was expected. This artifact was not present using positron emission tomography to its full potential, i.e. dynamic positron emission tomography. Dynamic positron emission tomography studies provide quantitative data about perfusion. The posterolateral artifact during static positron emission tomography imaging with [^{13}N]ammonia might be explained by the metabolism of [^{13}N]ammonia because static images are obtained late after injection of [^{13}N]ammonia while dynamic perfusion measurements use data early after the injection of [^{13}N]ammonia. The investigations in chapter 2 are thus performed using dynamic positron emission tomography. In chapter 2, the relation between myocardial perfusion and severity of heart failure was investigated. Brain (or B-type) natriuretic peptide was measured as an objective measure of heart failure. Patients with left ventricular dysfunction without signs of heart failure (i.e. normal brain natriuretic peptide) were compared to patients with left ventricular dysfunction with signs of heart failure (i.e. elevated brain natriuretic peptide). Perfusion was studied at rest and after administration of dipyridamole to assess myocardial perfusion reserve. Furthermore, myocardial perfusion was measured during endothelial function testing using the cold pressor test. Although it was initially expected that patients with higher BNP would show more abnormalities, no clear differences in endothelial function and myocardial perfusion reserve were found; endothelial dysfunction and myocardial perfusion reserve were equally affected in patients with and without elevated brain natriuretic peptide. These results might suggest that abnormalities in myocardial perfusion precede the development of heart failure in patients with left ventricular dysfunction.

In chapters 3, 4 and 5 measurements of myocardial b-adrenoceptor density are described. Chapter 3 is a review discussing the measurements of myocardial b-adrenoceptor density and focuses primarily on *in vivo* measurements in humans. Although much has been learned about the role of the b-adrenoceptor in cardiac function from *in vitro* studies, these measurements are by definition a limited reflection of the *in vivo* condition and because of their invasive nature do not allow longitudinal and regional assessment of myocardial b-adrenoceptors in humans. The development of new methods to measure b-adrenoceptors *in vivo* might help us to further understand b-adrenoceptor function and could add prognostic information and assist in clinical decisions about therapeutic interventions. Positron emission tomography studies measuring b-adrenoceptor density are promising and support and extend the results of *in vitro* studies. Positron emission tomography measurements of b-adrenoceptor density show clear differences between patients with heart failure, showing a reduced b-adrenoceptor density, and patients without heart failure. Furthermore, there seems to be a reduced b-adrenoceptor density in patients with hypertrophic cardiomyopathy, a disease that can progress to heart failure. In patients with diseases that do not progress to heart failure b-adrenoceptor density was equal to measurements in healthy volunteers, except for patients with arrhythmogenic right ventricular cardiomyopathy. In Chapter 4 the regional quantification of b-adrenoceptor density is investigated. It shows that regional variations in b-adrenoceptor can be reliably assessed. A parametric polar map approach combined with different filters was used to assess b-adrenoceptor density in 576 segments of the left ventricle. Reliable results (more than 95% of the segments having reliable values) were obtained in all subjects investigated; 9 volunteers and 4 patients. The method might be useful in the investigation of cardiac diseases in which a regional variation in b-adrenoceptor density may be expected. The studies in chapters 3 and 4 were performed with the radioligand [^{11}C]CGP 12177. Since the radiochemical synthesis of [^{11}C]CGP 12177 is very demanding a new tracer was developed, (S)-[^{11}C]CGP 12388. Chapter 5 shows that positron emission tomography with (S)-[^{11}C]CGP 12388 is applicable for the measurement of myocardial b-adrenoceptor density in patients. A highly significant reduction in b-adrenoceptor density was found in patients with idiopathic dilated cardiomyopathy compared to healthy volunteers. With the introduction of (S)-[^{11}C]CGP 12388, positron emission tomography could gain a more prominent role in the pathophysiological investigation of the b-adrenoceptor *in vivo*.

Chapters 6 and 7 describe the measurement of myocardial contractile reserve in patients with heart failure. Chapter 6 is a review describing various imaging methods and stress protocols to assess myocardial contractile reserve in a non-invasive way. In contrast to left ventricular performance measurements at rest, myocardial contractile reserve indices appear to be a better parameter of the functional status of the heart and seem to be a new prognostic marker in heart failure. The exploration of pathophysiologic mechanisms of heart failure and the assessment of the effect of therapeutic interventions may be facilitated by these new diagnostic opportunities. In chapter 7 one of the techniques described in chapter 6 is used to assess myocardial contractility in patients

with idiopathic dilated cardiomyopathy. A majority of patients with idiopathic dilated cardiomyopathy showed myocardial regions with a decreased wall motion during increased demand, i.e. an ischaemia-like myocardial contractile response during dobutamine stress echocardiography, which is generally observed in patients with ischaemic heart disease. These observations support the concept that an energy mismatch between demand and supply might play a pathophysiological role in idiopathic dilated cardiomyopathy.

DISCUSSION

The studies presented in this thesis provide further evidence for the hypothesis that myocardial ischaemia plays a pathophysiological role in the progression of left ventricular dysfunction to heart failure, both in patients with and without coronary artery disease. A misbalance between demand and supply may lead to (progression of) heart failure. A vicious circle may develop in which ischaemia leads to heart failure and heart failure to ischaemia (Figure 1).

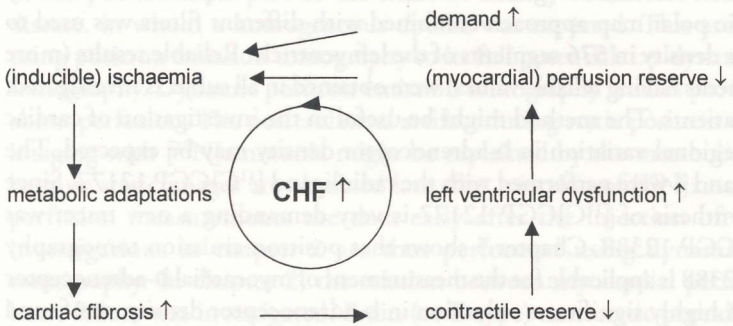

Figure 1. Vicious circle of ischaemia leading to heart failure and heart failure leading to ischaemia.

In patients with coronary artery disease who show signs of left ventricular dysfunction but no signs of heart failure, myocardial perfusion (i.e. supply) was seriously affected, comparable to patients who presented with signs of heart failure. This suggests that myocardial perfusion abnormalities could precede the progression of heart failure. Patients with idiopathic dilated cardiomyopathy showed dobutamine stress (i.e. higher demand) induced regional wall motion abnormalities, which in patients with coronary artery disease are interpreted as a sign of ischaemia. The (regional) abnormalities in contractility might be caused by a downregulation of b-adrenoceptor, which can be studied *in vivo* using positron emission tomography.

Further investigation is needed to provide more insight into the pathophysiological mechanisms involved in the development and progression of heart failure. Abnormalities in myocardial perfusion, b-adrenoceptor density and myocardial contractility should be further explored. A relation between these observations can be investigated combining the different measurements to provide more evidence that ischaemia plays a key role in the progression of heart failure, even in patients without coronary artery disease. Furthermore, follow up studies might provide us with information if patients with more abnormalities in myocardial perfusion and contractility have a greater risk to develop heart failure.